This patient's weight increased from 135¼ pounds to 140½ pounds, but the glycosuria was not at all influenced. His general health and ability to work were markedly improved.

The third patient was a business man, aged sixty-four years, who had had a mild diabetes for about five years, his tolerance being 60 grams of white bread in twenty-four hours. This was increased to 90 grams of bread after an extended course of exercises.

SOME ASPECTS OF THE CLINICAL STUDY OF THE RESPIRATION: THE SIGNIFICANCE OF ALVEOLAR AIR ANALYSES.[1]

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One of the most striking developments in clinical medicine during the last decade has been the gradual substitution of the physiological for the anatomical point of view. Up to within a comparatively few years the chief basis of medicine was pathological morphology, and the chief aim of diagnosis was to determine the anatomical changes in the diseased organs. Recent advances in physiology and in biological chemistry, however, have exerted a profound influence on the attitude of the clinician, and have impressed on him the importance of approaching his subject from a much broader aspect. The problem of diagnosis is now not so much to discover what a given organ may look like, but what it is doing or what it is able to do. Pathological physiology is becoming more and more an object of investigation, and such terms as "functional tests" and "functional diagnosis" are already current in medical phraseology.

The application of the methods of physiology has already produced an abundant harvest of results in several fields. The study of polygraphic tracings and of electrocardiograms, both in man and in experimentally produced conditions in animals, has quite altered our conceptions of heart disease. New clinical conditions have been differentiated, and processes long recognized have been explained. In renal diseases the "functional studies" have thrown new light on the various types of nephritis, their course, prognosis, and treatment. Some progress has been made in the investigation of hepatic function in disease, but as yet, unfortunately, little of great clinical significance has been brought out. On the subject of respiration a large amount of important work has already been done. The greater part of this has had to do directly with the study of metabolism, of oxygen intake, and carbon dioxide output and their relation to heat production under various conditions. Until comparatively recently very little attention has been paid to the abnormalities of respiration itself, but the development of a more comprehensive knowledge of the physiology of respiration and the adaptation of new physiological and chemical methods have opened up fresh paths to clinical investigation.

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[1] Read before the Springfield Academy of Medicine, March 9, 1915.

From the point of view of clinical medicine some of the most significant of the recent investigations on the physiology of the respiration have been those dealing with the determination of the normal stimulus to respiration. Among the older physiologists one school held that the respiratory centre was stimulated by a lack of oxygen, while their opponents claimed that it responded to an excess of carbon dioxide in the blood. The work of Haldane and Priestley,[2] in 1905, settled the problem for the time being and seemed to prove conclusively that carbon dioxide is the effective stimulus to respiration. Their experiments showed that the respiratory centre is extremely sensitive to changes in the tension of the carbon dioxide in the blood. A rise of 0.2 per cent. in the carbon dioxide of the alveolar air was sufficient to double the pulmonary ventilation, while a fall below the normal resulted in the production of apnea. Subsequent work, especially that of Winterstein[3] and of Hasselbalch[4] showed that the action of carbon dioxide as a stimulus to respiration is not specific, but that it depends on the fact that carbon dioxide is an acid. Any other acid can replace carbon dioxide wholly or in part as the stimulus. Indeed, it has been definitely demonstrated that the respiration depends on the reaction of the blood, or, as it is technically called, on the hydrogen-ion concentration of the blood. Under normal conditions the reaction of the blood is very slightly on the alkaline side of the neutral point. Any tendency toward an increase in the acidity, whether it be caused by an accumulation of carbon dioxide, or of any other acid, acts as a stimulus to the respiratory centre and increases the ventilation of the lungs. Even the increase of respiration, which is caused by an insufficient supply of oxygen reaching the tissues, may be explained by this same mechanism, for one of the results of imperfect oxidation is the incomplete combustion of acid products of metabolism, and these intermediary metabolites, insofar as they are acids, may form a part of the respiratory stimulus.

Since, then, the chemical control of the respiration depends on the reaction of the blood, it will be readily seen that in order to understand the pathological changes in respiration one must bear in mind the conditions which regulate the reaction of blood. Henderson[5] has said that the normal reaction of blood is, like the normal body temperature, one of the important physiological constants. All modern work bears this out. The chemical processes within the body, and especially all enzyme reactions, proceed most advantageously at an optimum hydrogen-ion concentration, and for many the range of reaction through which they can function is a narrow one. Life itself depends on the maintenance of the reaction of blood and tissues within very small normal limits. Undoubtedly the fundamental problem is that of the maintenance of the normal reaction within the tissue cells, for in all probability most of the important chemical processes by which metabolism is carried on are intracellular, or at least are the result of the actions of substances formed within the cells, whose very formation and elimination into the blood depends on the balance of acid and alkali within the cell. At the present time there are no very refined methods of studying tissue reaction, though, as will be shown later, the so-called "alkali-tolerance" test seems to give a more or less rough index of any continued overproduction of acid in the body and of consequent exhaustion of the reserve alkali of the tissues. Until methods have been evolved which will lead us into the obscure field of cellular and of tissue metabolism we must be content with studies of the blood. The composition of the blood certainly depends in large part on the activities of the fixed cells of the tissues, and the newer investigations of the chemistry of the blood and of the intermediary products of metabolism which it contains are leading to a much more intimate knowledge of the chemical processes of the body than could ever be obtained by examinations of the excretions alone. In the maintenance of the normality of the tissue reaction the blood plays an important part. It carries bases to the tissues to replace those used in neutralizing acids, and it forms the medium by which the acid products of cellular activity are removed from the cell. Fortunately, however, in spite of the fact that carbon dioxide and other acid products of metabolism are continually passing into the blood, the organism is peculiarly well provided with means to preserve its normality. That the reaction of the blood is not affected by this addition of acids depends (1) on its chemical composition, and (2) on the means at its disposal for the rapid excretion of acids.

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[2] Jour. of Physiol., 1905, xxxii, 225.

[3] Arch. f. die ges. Physiol., 1911, cxxxviii, 167.

[4] Biochem. Ztschr., 1912, xlvi, 403.

The chemical composition of blood is such that it is ideally adapted for the preservation of a constant reaction. It contains large amounts of weak acids and their salts—carbon dioxide and sodium bicarbonate, monosodium phosphate and disodium phosphate—and a high percentage of proteids which have both basic and acid characteristics. To solutions which are made up of such combinations it is possible to add considerable quantities of acid without producing any marked change in the hydrogen-ion concentration. If, for instance, acid be poured into a solution consisting of monosodium and disodium phosphates, the balance between the two will be disturbed—there will be more of the monosodium phosphate and less of the disodium phosphate—but within rather wide limits there will be only a minimal alteration in the true reaction of the solution. Indeed, Henderson has shown that the balance of weak acids and salts in blood is such as to allow of the addition of the maximum amount of acid with the minimum alteration in reaction.

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[5] Science, 1913, N. S., xxxvii, 389.

The constancy of the reaction of blood is furthermore upheld by the means which the body has at its command for the excretion of acid. Non-volatile acids are excreted by the kidneys. Henderson[6] has drawn particular attention to the remarkable efficiency of the kidneys for their task. By some specific mechanism they are able to separate acid from bases, secrete an acid urine from an alkaline blood, and retain base in the body for the further neutralization of more acid. Volatile acids, and chiefly, of course, carbon dioxide, are excreted in the lungs. In the pulmonary capillaries carbon dioxide passes out of the blood into the air of the alveoli until the carbon dioxide tension in the blood equals that in the alveolar air. Thus the tension of the carbon dioxide in the alveolar air corresponds to that of the blood, and, as will be seen, it is an index of acidosis. In their function of excreting acid the kidneys may perhaps be regarded as the fundamental regulators of the reaction of the blood, but as the lungs are much more sensitive they can maintain extremely delicately the constancy of reaction by their control over the volatile acids.

Any rise in the acidity of the blood stimulates the lungs to increased ventilation. With moderate exercise there is an increased production of carbon dioxide in the tissues. If this is sufficient to affect the arterial blood to the respiratory centre, the pulmonary ventilation rises and more carbon dioxide is excreted. The same happens when air is rebreathed from a closed space. The carbon dioxide in the inspired air, and consequently in the alveoli, rises. This causes a rise of carbon dioxide tension in the blood and and an increased ventilation of the lungs. During severe exercises, lactic acid is produced more quickly than it is excreted by the kidneys, and Ryffel[7] has shown that it is increased in the blood.

Under such circumstances the lactic acid acts as a stimulus to respiration by increasing the acidity of the blood. The lungs respond, but in order to keep the hydrogen-ion concentration of the blood at its normal level there must be a reduction of the carbon dioxide below its normal. Thus associated with the rise in non-volatile acids there is a compensatory decrease in the carbon dioxide tension of the blood, and since the two correspond, in the carbon dioxide tension of the alveolar air. These conditions are indicated diagrammatically in Figs. 1 and 2.

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[6] Jour. Biol. Chem., 1911, ix, 403.

[7] Jour. Physiol., Proc. Physiol. Soc., 1910, xxxix.

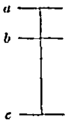

FIG. 1

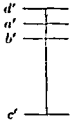

FIG. 2

In Fig. 1 the line *a–c* represents the acidity of normal blood; *b–c* is acidity due to non-volatile acids, and *a–b* is the acidity due to carbon dioxide.

Fig. 2 represents the conditions in acidosis due to a rise in the non-volatile acids, such as lactic acid in hard exercise or β-oxybutyric acid in diabetes, *b'–c'*, which is longer than *b–c* in Fig. 1, represents the increased acidity due to non-volatile acids. If the carbon dioxide remained unchanged, the acidity of the blood would be represented by the line *d'–c'*, an increase in the acidity of the blood which the organism could not withstand. In order to keep the acidity of the blood at its normal value, *a'–c'*, the rise in non-volatile acids is compensated for by a fall in carbon dioxide, so that the amount of carbon dioxide or, more accurately, the carbon dioxide tension, is reduced to *a'–b'*. Thus in conditions of acidosis the tension of the carbon dioxide in the blood or, what is the same thing, the tension of carbon dioxide in the alveolar air, gives an accurate index of the amount of the increase of non-volatile acid.

The demonstration that one of the chief functions of the respiration is to preserve the normal reaction of the blood, and that any increase in the acidity of blood acts as a stimulus to respiration, is of great importance in the consideration of pathological changes in the respiration. In the study of acidosis—of the increase of normal acids or the presence of abnormal acids in the blood—we possess a means of acquiring information concerning the stimulus to respiration and its variations in abnormal conditions. There are several general methods of approach by which one may find out about the formation of acids in the body. The examination of the urine with reference to its acidity, and to the presence of abnormal acids, while of a certain value, only tells about the acid which is leaving the body and does not necessarily give an accurate picture of conditions within the body. Of much more significance are studies of the blood itself. As has already been stated, the true reaction of the blood varies extremely slightly during life. Only in terminal conditions has any marked deviation from the normal been found. Thus in most clinical conditions one does not expect that an increase in the formation of acids in the body will cause any actual change in the reaction of the blood, but merely a shift in the usual balance between volatile and non-volatile acids. In the pathological conditions associated with acidosis there is usually an increase in non-volatile acids and a consequent fall in carbon dioxide. The evidence of the presence of such a state may be obtained from the study of the blood or of the alveolar air, for the carbon dioxide tension of the alveolar air is the same as that of the blood.

The determination of the hydrogen-ion concentration of the blood is a complicated procedure. On account of its color, the high percentage of protein, and the influence of the carbon dioxide the simple colorimetric methods which may be used in urine are not practicable. The direct determination can only be carried out by means of electrochemical methods, and the difficulties of the technic are considerably enhanced by the importance of measuring the blood at a known carbon dioxide tension.[8] Barcroft[9] has devised a method by which the acidity of the blood is determined from the affinity which the hemoglobin shows for combining with oxygen under standard conditions. Both of these methods involve a highly specialized technic, but fortunately a very valuable index of the conditions in the blood may be obtained quite simply by means of an analysis of the alveolar air.

Under normal conditions, at rest, the carbon dioxide tension of the alveolar air is fairly constant. It shows only slight variations in different individuals, and in the same individuals at different times of day. The normal diurnal variations depend chiefly on diet. Thus on a pure carbohydrate diet the carbon dioxide extension is at a high level, while on a diet consisting largely of proteid or during starvation the tension tends to be lower. The normal variations, however, involve only a few millimeters and do not detract from the value of the determination in pathological conditions.

Samples of alveolar air may be obtained by several methods:[10] The first to be introduced was that of Haldane. In this method the subject gives a long, deep expiration into a piece of rubber tubing about four feet long. At the end of the expiration the entrance of the tubing is closed by the subject's tongue or by some form of valve, so that the expiration is held in the tube. By means of a small side tap near the mouth-piece, 25 to 50 c.c. of the air which constitutes the last portion of the expiration are withdrawn into a mercury filled gas pipette and subsequently analyzed. The last

[8] Arch. Int. Med., 1914, xiv, 236.

[9] The Respiratory Function of the Blood, 1914, Camb. Univ. Press.

[10] Arch. Int. Med., 1914; xiii, 497.

part of the expiration, particularly if the expiration is at least 600 c.c. deep, comes from the alveoli of the lungs, and if the expiration is sufficiently rapid its composition remains practically unchanged in its passage outward. In the hands of trained persons this method gives reliable results, and the figures obtained for carbon dioxide tension probably agree very closely with that of the arterial blood. Even with untrained subjects it is frequently possible to get satisfactory samples, but as it is necessary to have a very deep and rather rapid expiration there are many times when the method is unreliable. This is especially apt to be the case with persons of low intelligence or with patients who are sick and unable or unwilling to give a complete expiration. In such instances the method of Plesch as modified by Higgins[11] gives excellent results. A large series of observations made during the last two years at the Peter Bent Brigham Hospital with this method has demonstrated its simplicity and reliability in a considerable variety of clinical conditions. The method is based on the principle that if the subject breathes into and out from a closed space of suitable size for a definite period of time the diffusion of gases will be such that the composition of the air in the closed space will be similar to that in the lungs. In practice the nose is closed with a clip and the patient breathes through a mouth-piece, which is connected with a three-way valve leading to the outside air or into a rubber bag. The subject begins by breathing the outside air. At the end of an expiration the valve is turned so that the subject is connected with the rubber bag which contains about 1 liter of air. He takes four or five rather deep and slow respirations from the bag in twenty or twenty-five seconds. At the end of the last expiration the valve is again turned and the subject connected with the outside air. The bag, which is closed off by the same maneuver, contains air which is of the same composition as the air in the alveoli. Samples are then taken from the bag for analysis. The figures obtained for carbon dioxide tension by this method are somewhat higher than those obtained by the Haldane method, and they probably represent more nearly the tension of the carbon dioxide in the venous blood than in the arterial blood. In physiological studies the difference would be important, but in most clinical work the Plesch method gives results that fulfil all the necessary requirements. There are two chief sources of error in the method: The figures for carbon dioxide tension are too low if the respirations are very rapid and shallow, so that proper diffusion of gases does not take place. The results are too high if the subject is permitted to breathe from the bag for a period which exceeds in length one complete cycle of the circulation or approximately forty seconds. In general, however, constant and reliable results are obtained with little experience. Three observations are usually made, and the analysis of the samples should agree within 2 mm. carbon dioxide tension. Occasionally one of the three varies so far from the mean that it has to be discarded. The analysis of air for carbon dioxide is extremely simple. By means of the Haldane gas analysis apparatus it can readily be completed in about four minutes. The figures for the normal tension of carbon dioxide in the alveolar air vary from about 38 to 41 mm. by the Haldane method and from 40 to 45 mm. by the Plesch method.

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[11] Pub. No. 203, Carnegie Institution of Washington, 1915, p. 168.

RESULTS OF THE STUDY OF PATHOLOGICAL CONDITIONS. DIABETES. One of the first diseases in which it was recognized that acidosis played an important part and the disease in which the effect of acidosis on the respiration is most definitely manifested is *diabetes*. Probably on account of the incomplete or imperfect combustion of fats in severe cases of diabetes there may accumulate in the organism large amounts of β-oxybutyric acid, aceto-acetic acid, and acetone—substances which under normal conditions would be completely burned to water and carbon dioxide. This abnormal production of acids may go on for a long time without giving rise to any clinical symptoms, but when it reaches an extreme grade it becomes the most prominent feature in the case and eventually brings on the well-known clinical picture of "air hunger" and coma. During the early stage, while the production of acids is not excessive, the bases in the tissues and in the blood are sufficient to neutralize them, and their excretion is accomplished by the kidneys. At this period the ordinary mechanisms of the body are amply able to cope with the acidosis, so that there is no tendency for the reaction of the blood to be disturbed. If the condition continues, however, and the amount of acid increases, the reserve supply of base in the tissues will become exhausted in the attempt to neutralize the acid. The blood itself will be able to take up a considerable amount of acid without any effect on its true reaction, but beyond a certain point the addition of more acid will tend to cause a shift in the reaction of the blood. This increase in acidity will act as a stimulus to respiration and the normal reaction of the blood will be maintained by an increased pulmonary ventilation and a lowering of the carbon dioxide tension of the blood. The balance in the blood will be disturbed and there will be an increase in non-volatile acids with a corresponding drop in the tension of the carbon dioxide in the blood and in the alveolar air. This is the beginning of serious acidosis. The reserve supply of base in the tissues has been used up, the regulatory mechanism in the blood has begun to break down, and the organism is calling on its last reserves. If the condition progresses there will be a steady fall in the carbon dioxide tension of the blood until the symptoms of poisoning assert themselves. Finally the production of acids becomes so great that even kidneys and lungs together are unable to excrete enough acid to keep the reaction of the blood within its normal bounds. The increased acidity of the blood stimulates the respiratory centre to greater efforts, and there results the enormous ventilation marked by the deep, rapid breathing which is so well termed "air hunger." Unless the formation of acids is reduced or their neutralization is brought about by some means, death from acidosis will ensue.

There are several methods by which it is customary to follow the course of acidosis in diabetes. Since these are usually tests applied to the urine they give evidence only of the amount of acid which is being excreted from the body. They give extremely unreliable information as to the amount of acid which is being formed in the body and as to the amount which is accumulating in the body. These latter are, after all, the factors of importance. What one wants to know is not how much acid the organism is getting rid of, but how much it is retaining, for it is the retained acid that is the source of danger. The commonest tests applied in diabetic acidosis are the qualitative tests for acetone and aceto-acetic acid. The attempt is usually made to get a general idea of the amount of each acid excreted from the degree of the reaction. The value of these tests is limited both by the fact that they give no conception as to the excretion of β-oxybutyric acid and because the information they do give may throw so little or such false light on the actual conditions within the body that an implicit reliance on them becomes extremely dangerous. In severe acidosis, and even in diabetic coma, the ferric chloride reaction is sometimes very weak. After the administration of alkali the reaction frequently becomes much more intense. On the one hand the patient may have been in grave danger from acidosis at the time when the urine showed evidence of a very small aceto-acetic acid excretion, while, on the other hand, the increase of the excretion of aceto-acetic acid may have been accompanied by a return to conditions within the body which are comparatively normal. Not infrequently one hears of cases of diabetes that went suddenly into coma without any previous warning. These are probably instances in which there has been an accumulation of acid in the body without any very marked excretion in the urine, so that even careful urine examinations have failed to call attention to the impending danger. It seems probable that the ammonia excretion is the best index which can be obtained from the urine, but even this will fail to give a correct quantitative picture in certain instances. As Poulton[12] has pointed out the ammonia in the urine depends (1) on its production in the body, and (2) on its excretion by the kidneys, and if either of these functions is disturbed the values obtained will fail to give a true estimate of the acidosis. It is, moreover, the total amount of ammonia excreted in twenty-four hours that is of importance, and in many cases it is impossible to obtain complete collections of urine. Even at best the method does not allow one to obtain the immediate information that is so often desirable. The determination of B-oxybutyric acid in the blood would be of great value, but the methods now available are difficult and require a considerable amount of time. On the whole the determination of the carbon dioxide content of the alveolar air bids fair to prove one of the most useful aids in judging of the severity and course of acidosis. It is comparatively simply done, and it gives accurate information of the conditions which prevail in the blood at any given time. The presence of a positive ferric chloride reaction in the urine shows that abnormal acids are being formed, but if at the same time the alveolar air remains normal it is probable there is no immediate danger to be feared. When the alveolar carbon dioxide falls below normal the danger zone is being approached. Values between 35 and 30 mm. may be taken as indicating the development of a considerable acidosis, and one that demands treatment, but they need not give rise to the fear of any serious complication. Carbon dioxide tensions between 30 and 20 mm. are of much more significance, and are to be regarded as evidence that the patient is nearing the border-line and must be watched with great care. A constantly falling carbon dioxide tension is a serious warning, and is of great prognostic value. If the carbon dioxide tension is down to 20 mm. or lower the patient has reached a state in which coma may suddenly appear. Indeed, Poulton[13] who has given this matter considerable attention, states that "values of below 2.5 per cent. (about 18 mm.) indicate the early onset of coma, possibly within forty-eight hours unless drastic measures are taken." Analyses of the alveolar air in a case which was recently admitted to the Peter Bent Brigham Hospital in diabetic coma showed that the carbon dioxide tension varied between 6 and 10 mm. Very similar figures are given by Poulton for his cases in coma.

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[12] Proc. Roy. Soc. Med., 1914, vii (Med. Sec.), 171.

Besides being an aid to prognosis the alveolar air determinations may be of distinct value as a guide to therapy. When alkali is being administered the urine gives little evidence as to the results that are being accomplished until its reaction has been changed. As has already been stated, the ferric chloride reaction often becomes more intense. The alveolar air, however, gives an accurate indication of the effect of treatment. As the acidosis is overcome the carbon dioxide tension rises until it reaches normal. At this point the patient is out of immediate danger, but frequent examinations will be necessary to keep one informed as to when vigorous treatment may have to be instituted again. This effect of the alkali is usually rapid and complete in cases of mild or moderate acidosis, but if the acidosis has developed to an extreme grade, a point is apparently reached beyond which the administration of alkali produces little or no permanent change in the clinical picture or in the composition of the alveolar air. Thus in the patient with diabetic coma mentioned above, in spite of the administration of considerable amounts of sodium bicarbonate, both by mouth and intravenously, no permanent beneficial effect was produced. On admission, shortly after he had gone into coma, the alveolar carbon dioxide was 6.71 mm. After vigorous treatment it rose to 10.7 mm. on the next day, and synchronous with this his mental condition improved so that he was recognizing his friends. On the following day the carbon dioxide tension was 12.9 mm. and there was further subjective improvement. During the night, however, his condition suddenly changed and he went rapidly into a diabetic coma in which treatment was without avail and which was fatal within twenty-four hours. It is, of course, possible that much larger amounts of alkali should have been given, and perhaps such treatment would be safe if it were guided by alveolar-air determinations.

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[13] Proc. Roy. Soc. Med., 1914, vii (Med. Sec.), 171.

CHRONIC NEPHRITIS. Among the many theories which have been brought forward to explain the clinical picture of uremia is that which acounts for it on the basis of an acidosis. As early as 1888 von Jaksch[14] suggested that this was the underlying factor. During the last few years this theory has again been brought into prominence by the work of Straub and Schlayer,[15] on the alveolar air in advanced cases of nephritis, and by the studies of Sellards[16] and Palmer,[17] both of whom showed that a mild grade of acidosis may be present comparatively early in the course of the disease. Evidence of the existence of an acidosis in moderate cases of chronic nephritis is based in large part on the so-called "alkali-tolerance" test of Sellards. If a normal individual be given sodium bicarbonate the urine will become alkaline after the ingestion of 5 grams or, at the most, of 10 grams. If an acidosis is present a much larger amount of alkali will be needed to produce this change in reaction. The probable explanation of this is that during the development of the acidosis the reserve supply of base in the tissues is being drawn upon to neutralize the acids which are produced. When more base is supplied to the body by the administration of alkali this is first used to restock the depleted stores in the tissues before it is allowed to accumulate in the blood and bring about a change in the reaction of the urine. If this theory of the mechanism by which the body disposes of alkali, when it is administered to it during acidosis is correct—and there is every reason to suppose that it is—then it will be seen that the "alkali-tolerance" test may serve as an important index of what may be termed "tissue acidosis." Since the acid products of metabolism are largely formed within the cells, it is evident that "tissue acidosis" may occur before there will be any marked change in the blood. Probably only after large amounts of acid have been produced in the cells, and the supply of bases in the cells has been to a considerable extent used up, will unneutralized acid pass into the blood, and only after the blood itself has neutralized much of this will the composition of the blood be changed in the sense of an increased acid reaction. Thus quite a degree of acidosis may exist in the body without affecting the blood so as to cause a fall in the carbon dioxide tension of the alveolar air.

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[14] Ztschr. f. klin. Med., 1888, xiii, 350.

[15] München. med. Wchnschr., 1912, lix, 569.

[16] Johns Hopkins Hosp. Bull., 1912, xxiii, 289; ibid., 1914, xxv, 141.

[17] Med. Communication, Massachusetts Med. Soc., 1913, xxiv, 133.

The "alkali-tolerance" test throws much light on the time of the development of acidosis in renal disease and on its underlying causes.[18] In early cases of nephritis, such as those in which the phthalein test shows a normal excretion, even when they are accompanied by a pronounced hypertension, it is unusual to find any evidence of acidosis. The urine is readily made alkaline by the administration of 5 to 10 grams of sodium bicarbonate. As cases become more severe and the phthalein excretion begins to drop below the normal level the "alkali-tolerance" test is likely to become increased, so that 15 to 20 grams of sodium bicarbonate are required to change the reaction of the urine. As the nephritis progresses and phthalein excretion continues to decrease the "alkali tolerance" rises until, in very advanced cases, it may be extremely difficult to administer sufficient base to make the urine alkaline. The development of the acidosis thus bears a definite relationship to the functional capacity of the kidney as indicated by the phthalein test. The fall in phthalein output runs fairly parallel with the rise in non-protein nitrogen content of the blood, and it is natural to refer both of these, and also the acidosis which accompanies them, to the decrease in the excretory power of the kidney. The acidosis of chronic nephritis is thus due to retention. While in diabetes the acidosis is the result of increased formation of acids, in nephritis it apparently depends on the inability of the organism to get rid of even a normal amount of acid. Whether there is also in nephritis a production of acids which exceeds the normal is as yet an uncertain question. The experimental work of Mosenthal,[19] which seems to show that a toxic destruction of protein is one of the accompaniments of nephritis, would favor such a view, for it is well known that proteids give rise to large amounts of acid-combustion products.

The urine in nephritis gives little information as to the acidosis within the body -even less than does the urine in diabetes. The hydrogen-ion concentration may be high, but it rarely exceeds the normal limits, and high values are by no means constant. The ammonia in the urine may not be increased, and is a comparatively unimportant index, as much of it may be retained with the other nitrogenous decomposition products. The ferric chloride reaction if positive is usually weak. The acidosis of nephritis is not due to the acetone bodies, but as to what acids are retained in the body little is known.

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[18] Results to be published in detail in a separate communication.

[19] Arch. Int. Med., 1914, xiv, 844.

While urine analysis is of limited significance in determining the grade and character of the acidosis in nephritis, much can be gained from observations on the alvolar air. A study[1] of about 50 cases in all stages of the disease permits of several general deductions on the manner and extent of its development. In the early stages of the disease there is no accumulation of non-volatile acids in the blood such as to cause a deviation of the tension of the alveolar carbon dioxide from the normal. Even after the phthalein excretion falls below normal, and after the "alkali-tolerance" test shows evidence of a considerable degree of "tisssue-acidosis," there is rarely any change in the alveolar air. Insofar as the acids are not excreted by the kidney they are apparently taken up by the blood, but the amount is not sufficient to cause any change in the reaction of the blood. At the time when the phthalein excretion is very low, and more often when there is no phthalein excretion, one frequently begins to find a drop in the alveolar carbon dioxide tension. This, however, is not a constant finding, as one patient with no excretion of phthalein and with non-protein blood nitrogen up to 90 mg. per 100 c.c. of blood had an alveolar carbon dioxide tension of 40.3 mm. ten days before she died. The majority of patients have a slight or moderate decrease of carbon dioxide, with values ranging from 37 to 25 mm. Such figures may be found during the development of uremia, but when the condition advances to coma the acidosis is frequently of higher grade. Nevertheless, in advanced uremia the alveolar carbon dioxide may not be below 30 mm. One patient had a carbon dioxide tension of 33.8 mm. and another of 24.4 mm. on the day before death. In certain cases, however, the onset of uremia is accompanied by the occurrence of a sudden and severe acidosis. In two instances the carbon dioxide fell to 4.59 and 19.1 mm. respectively. Both of these patients presented the clinical picture which is seen in diabetic coma, and their respiration was increased so that it amounts to a true "air hunger." The former died on the day after the alveolar air was examined. The latter was unusually interesting in the response shown to alkali therapy. The patient was a woman, aged forty-five years, with a history of nephritis going back for several years. Her blood-pressure was about 200 mm., and the non-protein nitrogen in her blood had risen to 90 mg. per 100 c.c. of blood. For over a month the phthalein test had shown practically no elimination of the dye in the urine. In spite of the very advanced nephritis her general condition remained fair, and except for headache there was no evidence of uremia until January 11. On this day she first began to complain of being short of breath. The alveolar carbon dioxide was 19.1 mm. tension. Turning over in bed caused marked dyspnea. Two days later, January 13, the patient was unconscious and her respiration was slow, but so deep as to be quite typical of "air hunger." The alveolar air was not taken at this time, but 300 c.c. of 4 per cent. sodium bicarbonate solution were given intravenously. On the following morning the carbon dioxide tension was 23.4 mm. This indicated a marked acidosis, and as the "air hunger" persisted, a further intravenous injection of 700 c.c. was given later in the day. When the patient was seen on the next morning the clinical picture had entirely changed. She was quite conscious, recognizing every one, but was greatly nauseated and looked very sick. The "air hunger" had disappeared, and the respiration was shallow, slow, and irregular, with rather prolonged periods of apnea. The alveolar carbon dioxide tension had risen to the normal value of 41.5 mm. On the next morning it had fallen to 36.9 mm. Respiration was perhaps slightly deeper, but did not suggest "air hunger." There were occasional deep, sighing breaths. Her sensorium was clouded, but she was conscious and responded fairly well to questions. In an attempt to ward off the further development of acidosis, 375 c.c. of 5 per cent. sodium bicarbonate were given intravenously, but in spite of this the alveolar carbon dioxide had next day dropped to 25.1 mm., her respiration was deeper and more rapid, and she was becoming unconscious again. On January 17 she was comatose and had begun to have convulsions. Respiration was deep, irregular, and stertorous. It was extremely difficult to get satisfactory samples of alveolar air. Those obtained showed a carbon dioxide tension of about 30 mm. Another intravenous alkali injection was without effect, and the patient died on January 18. This case is reported in considerable detail because it shows unusually well the development of a marked acidosis during uremia, which was clinically similar to the typical acidosis of diabetes. The existence of the acidosis was confirmed by the alveolar-air examinations, with its response to alkali treatment was, though temporary, most striking.

The demonstration of the occurrence of acidosis in chronic nephritis is a comparatively simple matter. It is much more difficult to form a correct opinion as to the part which the acidosis plays in the symptomatology of nephritis and of uremia. To do so on the basis of the knowledge now at our command would probably be impossible. So complex are the changes in the blood and tissues which may result from the inability of the kidneys to excrete the waste products of metabolism, and so many are the substances which may accumulate in the body, that it is not easy to determine what effects any one of them may produce. However, in a condition like uremia it is most important to separate out the constituent causative elements, for only by so doing will its pathology eventually become clear. It is, of course, possible that the accumulation of acid and the consumption of the supply of base in the tissues, even as it occurs during the early period of retention, may have some abnormal effect on the fixed cells. If there is any such it is obscure, and at present there is no evidence as to how it acts. In the later stages, especially with the change in the blood and the fall in the alveolar carbon dioxide, the acidosis, as will be shown later, seems to bear a relation to the occurrence of dyspnea. The association of acidosis and uremia is of special interest. The extent to which acidosis appears in and causes the symptom-complex of uremia is a variable one, but it seems to be an element in most if not all cases. In one group of patients uremia may exist for a considerable period and the acidosis be of a grade that produces a high "alkali tolerance," but only a slight depression of the alveolar carbon dioxide. With the onset of coma the alveolar carbon dioxide will perhaps drop somewhat, but there is no development of "air hunger," nor does the carbon dioxide tension reach the values seen in diabetic coma. Other patients present a picture in which the acidosis is in the foreground. With the onset of severe uremia at or just before the time when coma sets in the clinical signs of acidosis present themselves, the respiration is similar to that in diabetic coma, and the alveolar carbon dioxide will be found to have dropped to the very low values which obtain in that condition.

The single experience cited above shows that this type of case will, at least sometimes, respond to alkali treatment. The response will probably only be temporary, for uremia is not acidosis alone, and even if the acidosis is successfully combated, there are other factors which must eventually bring about death.

CARDIAC DYSPNEA. Some of the newer methods for studying the physiology of the respiration have also been applied in an attempt to explain the etiology of cardiac dyspnea. While there are as yet many points that are uncertain, progress has been made, and the facts so far determined are of importance to the clinician. Lewis, Barcroft, and their collaborators were the first to point out that in considering this problem one must recognize two groups of dyspneic patients. One of these consists of the pure cardiac cases. "These are usually young subjects with fresh or heightened color, and although cyanosis—slight, moderate, or deep—is present, dyspnea, as indicated by the rate of respiration, is not great. The respirations range from twenty-five to thirty-five per minute; orthopnea is present and the field of respiratory response is strictly limited."[20] The other group consists of elderly subjects with continuous dyspnea, often intensified for short periods, especially at night, without marked cyanosis, with Cheyne-Stokes breathing, an increased pulse rate, and a subnormal temperature. The clinical picture is essentially what is generally known as cardiorenal disease. Further studies have confirmed the desirability of differentiating these two groups, partly on account of their clinical symptomatology and partly because the cause of the dyspnea is not quite the same in both classes.

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[20] Quart. Jour. Med., 1915, viii, 97.

The group of pure cardiac cases with dyspnea consists chiefly of patients with valvular disease and acute decompensation. They are often extremely breathless when first brought to the hospital, but it is quite striking that severe dyspnea does not generally persist for long. After one or two days the respiration usually becomes much quieter, although orthopnea may continue for some time. While dyspnea is produced by very slight exertion, they are comparatively comfortable as long as they are at rest in bed. In an attempt to obtain some information as to the cause of the dyspnea in this group of cases the alveolar carbon dioxide has been studied and the following facts obtained. At a time when the patients show no dyspnea while they are at rest, even though very slight exertion causes breathlessness, the alveolar air is perfectly normal. Very frequently during the period of dyspnea the alveolar carbon dioxide shows no evidence of acidosis. Indeed, the absence of acidosis is, according to Lewis and his associates, one of the characteristics of this type of case. Since they have failed to find any evidence of acidosis by using Barcroft's method for the blood, and since the dyspnea and the cyanosis seem to them to run nearly parallel, they believe that the dyspnea depends on poor oxygenation of the tissues. The studies at the Peter Bent Brigham Hospital, however, have demonstrated that in many cases at the time when the dyspnea is most severe the alveolar air analyses show a depression of carbon dioxide tension such as indicates a moderate grade of acidosis. Thus, two patients who entered the hospital with severe dyspnea and a high degree of cyanosis showed carbon dioxide tensions of 30.9 and 34.7 mm. respectively. A few days later, when they had regained compensation, the alveolar air had returned to normal. It is noteworthy that the phthalein tests, the non-protein nitrogen in the blood, and the blood-pressure were normal in these patients, so there is nothing to make one believe that there was any renal element in the case. These observations on the acidosis of cardiac dyspnea confirm the results of Beddard and Pembrey[21] and of Porges, Leimdörfer, and Markovici.[22]

Thus in the pure cardiac cases dyspnea may be present when the alveolar carbon dioxide is normal or when it is somewhat depressed. In other words, there may or may not be acidosis, and if there is any acidosis, it is usually present only during the very acute stage, after which it quickly disappears. In either case the dyspnea is probably correctly explained by Lewis as the result of insufficient oxygenation of the tissues. With the failing heart and slowing of the circulation, carbon dioxide may accumulate in the respiratory centre and stimulate it to increase the ventilation. If the condition of the circulation becomes so poor that the amount of oxygen reaching the tissues is greatly reduced there will be incomplete combustion of the substances formed during cellular metabolism and the accumulation of acids in the blood. These acids, acting as a stimulus to the respiratory centre, will increase the pulmonary ventilation so that the carbon dioxide tension will be reduced and the oxygenation of the blood will be improved. Since the kidneys are normal the excretion of acid will go on rapidly, and as soon as the circulation has readjusted itself the excess of non-volatile acids will be got rid of. Then the alveolar air will return to normal. In cases with sufficient passive congestion, however, to inhibit the renal functions, there may well be some temporary retention of acids.

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[21] British Med. Jour., 1908, ii, 580.

[22] Ztschr. f. klin. Med., 1913, lxxvii, 446.

The second type of dyspneic patients consists of those in whom the element of acidosis plays a more significant part. Lewis recognizes that in this group renal lesions are generally present and believes that the acidosis is connected with nephritis, but he apparently feels that the evidence is as yet too scanty to allow of their being definitely associated together. Our own studies have been on cases in whom the renal condition has been investigated as carefully as possible. Blood-pressure, phthalein tests, and determinations of the non-protein nitrogen of the blood all support the view that these are usually cases with extensive degenerations of the kidneys. Clinically, the patients are frequently elderly persons, often with the pallor of arterial or renal disease, with comparatively little cyanosis. Orthopnea is present, and particularly characteristic are sudden attacks of severe dyspnea occurring especially at night. The respiration is usually rather rapid, shallow, irregular, and very frequently Cheyne-Stokes in character. The patients are often dull or sleepy, dosing off during the periods of apnea, arousing suddenly, and sometimes having great distress during the periods of dyspnea. The urine is that of chronic nephritis and the blood-pressure is usually well above normal. The condition is most often a permanent one, lasting days, weeks, and even months before death. Less often there are transient or fairly prolonged intervals of a return to comparative comfort and health. In general, the condition indicates serious organic disease and the prognosis is bad.

Analysis of the alveolar air in this clinical condition shows that it is quite generally associated with a fall in the carbon dioxide tension. This decrease is not great, however, and the values, while sometimes reaching as low as 25 mm., are most frequently between 35 and 30 mm. In almost all the cases in which the symptom-complex has been clear cut and the acidosis evident the functional tests have shown that the kidneys were decidedly inefficient. Usually the phthalein output was measured as "traces" or "zero." It is thus quite natural, and probably correct, to conclude that the acidosis is due to an accumulation depending on incomplete excretion, and is of renal origin.

It is extremely difficult to decide how important a part the element of acidosis plays in producing the clinical symptoms of dyspnea in cardiorenal disease. In another clinical condition, such as diabetes, the same amount of acidosis as indicated by the alveolar air produces no gross changes in the respiration. In diabetes it is only when a much greater depression of the alveolar carbon dioxide has taken place that the breathing is affected, and even then a wholly different type of respiration results. The deep, regular respiration of diabetic acidosis is totally unlike the shallow rapid, irregular, periodic respiration of cardiorenal disease. If then the dyspnea of cardiorenal disease depends on acidosis alone it must be that there are other factors which modify the way in which the organism reacts. On the other hand, because the acidosis is not very great, one must not necessarily conclude that it is of no significance in the production of the dyspnea. Some observations recently finished indicate that it is of considerable importance.[23] Subjects have been allowed to breathe through valves attached to a so-called "closed-circuit apparatus." The expired air passes through two tanks and is subsequently rebreathed, so that the inspired air has a continually increasing content of carbon dioxide. By special arrangements the pulmonary ventilation of the subject is measured, and samples of the inspired air are taken at regular intervals for analysis. It has been found that normal individuals react in a fairly constant manner to the stimulus of the carbon dioxide in the inspired air. Thus when the carbon dioxide reaches a concentration of between 4.5 and 5.5 per cent. of the inspired air, the subjects are breathing so deeply that their initial ventilation has been doubled. Patients with cardiac disease, but who are compensated while at rest, react in a similar manner. Patients with decompensated cardiorenal disease, however, and with acidosis as indicated by the alveolar air, are much more sensitive to the carbon dioxide, and it is found that their ventilation may become doubled with only 2 or 3 per cent. carbon dioxide in the inspired air. It has already been shown that owing to the *peculiar com-*

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[23] To be reported in detail in a separate communication.